Clinical trial results:
Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD) (PRO2TECT - CORRECTION)

Summary

EudraCT number	2015-004265-81
Trial protocol	HU ES BG GB IT
Global end of trial date	04 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	AKB-6548-CI-0014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02648347
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Akebia Therapeutics, Inc.
Sponsor organisation address	245 First Street, Suite 1400, Cambridge, Massachusetts, United States, 02142
Public contact	Clinical Trial Information Desk, Akebia Therapeutics, Inc., +1 617-844-6128, trials@akebia.com
Scientific contact	Steven Burke, Chief Medical Officer, Akebia Therapeutics, Inc., +1 617-844-6128, trials@akebia.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the correction and maintenance of hemoglobin (Hb) in subjects with anemia secondary to non-dialysis-dependent chronic kidney disease (NDD-CKD).

Protection of trial subjects:

The study was conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), International Council for Harmonisation (ICH) guidelines, and all of the applicable United States Code of Federal Regulations 21 (US CFR 21 CFR Part 50 and 312).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 51
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Brazil: 120
Country: Number of subjects enrolled	Bulgaria: 83
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Mexico: 91
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	South Africa: 103
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Ukraine: 131
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 1061
Worldwide total number of subjects	1751
EEA total number of subjects	124

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	772
From 65 to 84 years	869
85 years and over	110

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 4708 subjects were screened for entry into the study. Of these, 1751 subjects were enrolled and randomized into the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Vadadustat

Arm description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Arm type	Experimental
Investigational medicinal product name	Vadadustat
Investigational medicinal product code	
Other name	AKB-6548
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg white to off-white, round, bi-convex film-coated tablets for oral administration with a starting dose of 300 mg/day

Arm title	Darbepoetin alfa

Arm description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Arm type	Active comparator
Investigational medicinal product name	Darbepoetin Alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

pre-filled syringes as an injectable solution for intravenous (IV) administration

Investigational medicinal product name	Darbepoetin Alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:
pre-filled syringes as an injectable solution for subcutaneous (SC) administration

Number of subjects in period 1	Vadadustat	Darbepoetin alfa
Started	879	872
Completed	670	675
Not completed	209	197
Consent withdrawn by subject	16	9
Death	174	167
Lost to follow-up	18	21
Missing	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Vadadustat

Reporting group description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Reporting group title	Darbepoetin alfa

Reporting group description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Reporting group values	Vadadustat	Darbepoetin alfa	Total
Number of subjects	879	872	1751
Age categorical			
Units:			
Age continuous			
Units: years			
arithmetic mean	65.2	64.9	
standard deviation	± 14.27	± 13.71	-
Gender categorical			
Units: Subjects			
Female	475	506	981
Male	404	366	770
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	22	23	45
Asian	48	37	85
Black or African American	188	172	360
Native Hawaiian or Other Pacific Islander	6	6	12
White	546	571	1117
Not Reported	5	6	11
Reported as Other	58	48	106
Multiple	6	9	15
Average hemoglobin			
Units: grams per deciliter (g/dL)			
arithmetic mean	9.113	9.142	
standard deviation	± 0.8015	± 0.7790	-

End points

End points reporting groups

Reporting group title	Vadadustat

Reporting group description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Reporting group title	Darbepoetin alfa

Reporting group description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Primary: Change in Average Hemoglobin (Hb) between Baseline and the Primary Efficacy Period (Weeks 24 to 36)

End point title	Change in Average Hemoglobin (Hb) between Baseline and the Primary Efficacy Period (Weeks 24 to 36)

End point description:

Change from Baseline was calculated as the Primary Efficacy Period value minus the Baseline value. The Primary Efficacy Period was comprised of Weeks 24 to 36. Analysis was conducted in members of the Randomized Population, comprised of all subjects randomized. Analyses of this population were based on the randomized treatment. Analysis was conducted using an analysis of covariance (ANCOVA) model with multiple imputation for missing data with Baseline hemoglobin concentration, region, and New York Heart Association congestive heart failure (NYHA CHF) class as covariates.

End point type	Primary

End point timeframe:

Baseline; Weeks 24 to 36

End point values	Vadadustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	879[1]	872[2]		
Units: milligrams per deciliter (mg/dL)				
least squares mean (standard error)	1.43 (± 0.046)	1.38 (± 0.047)		

Notes:

[1] - Randomized Population

[2] - Randomized Population

Statistical analyses

Statistical analysis title	ANCOVA with Multiple Imputation

Statistical analysis description:

Treatment comparison: Vadadustat minus Darbepoetin Alfa

Comparison groups	Vadadustat v Darbepoetin alfa

Number of subjects included in analysis	1751
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Least squares mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[3] - Establishment of non-inferiority was based on a margin of -0.75 g/dL applied to the difference in mean change of hemoglobin: vadadustat minus darbepoetin alfa

Secondary: Change in Average Hemoglobin (Hb) between Baseline and the Secondary Efficacy Period (Weeks 40 to 52)

End point title	Change in Average Hemoglobin (Hb) between Baseline and the Secondary Efficacy Period (Weeks 40 to 52)

End point description:

Change from Baseline was calculated as the Secondary Efficacy Period value minus the Baseline value. The Secondary Efficacy Period was comprised of Weeks 40 to 52. Analysis was conducted using an ANCOVA model with multiple imputation for missing data with Baseline hemoglobin concentration, region, and NYHA CHF class as covariates.

End point type	Secondary

End point timeframe:

Baseline; Weeks 40 to 52

End point values	Vadadustat	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	879[4]	872[5]		
Units: mg/dL				
least squares mean (standard error)	1.52 (± 0.052)	1.48 (± 0.053)		

Notes:

[4] - Randomized Population

[5] - Randomized Population

Statistical analyses

Statistical analysis title	ANCOVA with Multiple Imputation

Statistical analysis description:

Treatment comparison: Vadadustat minus Darbepoetin Alfa

Comparison groups	Vadadustat v Darbepoetin alfa

Number of subjects included in analysis	1751
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Least squares mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[6] - Establishment of non-inferiority was based on a margin of -0.75 g/dL applied to the difference in mean change of hemoglobin: vadadustat minus darbepoetin alfa

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 168 weeks

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs), defined as adverse events (AEs) that began (or pre-existing AEs that worsened) or or after the first dose, are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Vadadustat

Reporting group description:

Subjects were randomized to receive vadadustat at an initial oral dose of 300 milligrams per day (mg/day). Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on hemoglobin (Hb) level measurements every 4 weeks to maintain target Hb levels.

Reporting group title	Darbepoetin alfa

Reporting group description:

Subjects were randomized to darbepoetin alfa at an initial dose that was based on the current package insert for investigational sites in the United States (US), and the Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult subjects with chronic kidney disease not on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen.

Serious adverse events	Vadadustat	Darbepoetin alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	573 / 878 (65.26%)	561 / 870 (64.48%)	
number of deaths (all causes)	180	168	
number of deaths resulting from adverse events	177	165	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 878 (0.11%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 878 (0.11%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bladder transitional cell carcinoma			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelofibrosis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			

subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adrenal neoplasm			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Astrocytoma			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Astrocytoma, low grade			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric leiomyoma			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified recurrent			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant pleural effusion			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Marginal zone lymphoma			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic bronchial carcinoma			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-small cell lung cancer metastatic			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal squamous cell carcinoma stage 0			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Papillary renal cell carcinoma			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma recurrent			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer stage IV			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transitional cell carcinoma			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive urgency			
subjects affected / exposed	9 / 878 (1.03%)	11 / 870 (1.26%)	
occurrences causally related to treatment / all	1 / 9	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	6 / 878 (0.68%)	10 / 870 (1.15%)	
occurrences causally related to treatment / all	0 / 8	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	4 / 878 (0.46%)	9 / 870 (1.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	6 / 878 (0.68%)	7 / 870 (0.80%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	6 / 878 (0.68%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 878 (0.23%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			

subjects affected / exposed	4 / 878 (0.46%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 878 (0.00%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	4 / 878 (0.46%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	3 / 878 (0.34%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steal syndrome			

subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accelerated hypertension			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic rupture			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential hypertension			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery perforation			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery stenosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous perforation			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	23 / 878 (2.62%)	19 / 870 (2.18%)	
occurrences causally related to treatment / all	0 / 23	2 / 19	
deaths causally related to treatment / all	0 / 23	2 / 19	
Asthenia			
subjects affected / exposed	9 / 878 (1.03%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	6 / 878 (0.68%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Generalised oedema			
subjects affected / exposed	4 / 878 (0.46%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 878 (0.34%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chest pain			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Systemic inflammatory response syndrome			

subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental death			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac death			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest discomfort			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of device insertion			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Physical disability			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanoposthitis			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicocele			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	15 / 878 (1.71%)	18 / 870 (2.07%)	
occurrences causally related to treatment / all	0 / 27	0 / 20	
deaths causally related to treatment / all	0 / 1	0 / 4	
Pulmonary oedema			
subjects affected / exposed	8 / 878 (0.91%)	13 / 870 (1.49%)	
occurrences causally related to treatment / all	0 / 9	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			

subjects affected / exposed	7 / 878 (0.80%)	11 / 870 (1.26%)	
occurrences causally related to treatment / all	0 / 9	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pleural effusion			
subjects affected / exposed	6 / 878 (0.68%)	9 / 870 (1.03%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	8 / 878 (0.91%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	5 / 878 (0.57%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 2	
Respiratory failure			
subjects affected / exposed	6 / 878 (0.68%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	6 / 878 (0.68%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 878 (0.23%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	4 / 878 (0.46%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Device occlusion			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device adhesion issue			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	4 / 878 (0.46%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-alcoholic steatohepatitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	7 / 878 (0.80%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	5 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 878 (0.34%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 878 (0.34%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriogram carotid abnormal			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose decreased			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate irregular			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial pressure increased			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 878 (1.37%)	9 / 870 (1.03%)	
occurrences causally related to treatment / all	0 / 13	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hip fracture			
subjects affected / exposed	5 / 878 (0.57%)	7 / 870 (0.80%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 878 (0.23%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	3 / 878 (0.34%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	3 / 878 (0.34%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	2 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 878 (0.11%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site			

complication			
subjects affected / exposed	2 / 878 (0.23%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 878 (0.00%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula aneurysm			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iatrogenic injury			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratorhexis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lisfranc fracture			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic bone injury			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal dialysis complication			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpericardiotomy syndrome			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural dizziness			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural nausea			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract stoma complication			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access malfunction			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site pseudoaneurysm			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular injury			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal injury			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Gastrointestinal arteriovenous malformation			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous malformation			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	40 / 878 (4.56%)	39 / 870 (4.48%)	
occurrences causally related to treatment / all	1 / 50	0 / 48	
deaths causally related to treatment / all	0 / 2	0 / 4	
Acute myocardial infarction			
subjects affected / exposed	32 / 878 (3.64%)	27 / 870 (3.10%)	
occurrences causally related to treatment / all	0 / 34	1 / 30	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cardiac failure acute			
subjects affected / exposed	21 / 878 (2.39%)	24 / 870 (2.76%)	
occurrences causally related to treatment / all	0 / 25	1 / 28	
deaths causally related to treatment / all	0 / 3	0 / 3	
Cardiac arrest			
subjects affected / exposed	23 / 878 (2.62%)	16 / 870 (1.84%)	
occurrences causally related to treatment / all	1 / 23	1 / 16	
deaths causally related to treatment / all	1 / 21	0 / 11	

Cardiac failure			
subjects affected / exposed	15 / 878 (1.71%)	12 / 870 (1.38%)	
occurrences causally related to treatment / all	0 / 17	0 / 19	
deaths causally related to treatment / all	0 / 4	0 / 1	
Coronary artery disease			
subjects affected / exposed	12 / 878 (1.37%)	12 / 870 (1.38%)	
occurrences causally related to treatment / all	0 / 16	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	9 / 878 (1.03%)	12 / 870 (1.38%)	
occurrences causally related to treatment / all	0 / 9	0 / 14	
deaths causally related to treatment / all	0 / 7	0 / 10	
Atrial fibrillation			
subjects affected / exposed	11 / 878 (1.25%)	8 / 870 (0.92%)	
occurrences causally related to treatment / all	0 / 14	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	8 / 878 (0.91%)	9 / 870 (1.03%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	5 / 878 (0.57%)	8 / 870 (0.92%)	
occurrences causally related to treatment / all	0 / 5	1 / 8	
deaths causally related to treatment / all	0 / 3	1 / 4	
Angina unstable			
subjects affected / exposed	3 / 878 (0.34%)	8 / 870 (0.92%)	
occurrences causally related to treatment / all	0 / 3	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	3 / 878 (0.34%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiogenic shock			

subjects affected / exposed	6 / 878 (0.68%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 0	
Angina pectoris			
subjects affected / exposed	5 / 878 (0.57%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 878 (0.11%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			

subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 878 (0.00%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adams-Stokes syndrome			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial tachycardia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomegaly			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic left ventricular failure			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diastolic dysfunction			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis uraemic			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Right ventricular dysfunction			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic dysfunction			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	9 / 878 (1.03%)	12 / 870 (1.38%)	
occurrences causally related to treatment / all	0 / 10	0 / 13	
deaths causally related to treatment / all	0 / 2	0 / 1	
Metabolic encephalopathy			
subjects affected / exposed	9 / 878 (1.03%)	10 / 870 (1.15%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	7 / 878 (0.80%)	7 / 870 (0.80%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	5 / 878 (0.57%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			

subjects affected / exposed	7 / 878 (0.80%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	6 / 878 (0.68%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	3 / 878 (0.34%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain injury			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebral infarction			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			

subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 878 (0.00%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid arteriosclerosis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			

subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic neuropathy			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia infarction			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem haemorrhage			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain stem stroke			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar stroke			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral arteriosclerosis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral small vessel ischaemic disease			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Focal dyscognitive seizures			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic encephalopathy			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemic seizure			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemic seizure			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Migraine			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 878 (2.05%)	24 / 870 (2.76%)	
occurrences causally related to treatment / all	1 / 22	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			

subjects affected / exposed	12 / 878 (1.37%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 13	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	5 / 878 (0.57%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemoid reaction			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein thrombosis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blindness			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular degeneration			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	10 / 878 (1.14%)	10 / 870 (1.15%)	
occurrences causally related to treatment / all	0 / 16	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			

subjects affected / exposed	9 / 878 (1.03%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	1 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	3 / 878 (0.34%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 878 (0.46%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 878 (0.46%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pancreatitis acute			
subjects affected / exposed	3 / 878 (0.34%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic gastropathy			
subjects affected / exposed	3 / 878 (0.34%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			

subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dieulafoy's vascular malformation			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticulum intestinal			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Odynophagia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic necrosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux gastritis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			

subjects affected / exposed	5 / 878 (0.57%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal cyst			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic wound			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ingrowing nail			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
End stage renal disease			

subjects affected / exposed	292 / 878 (33.26%)	292 / 870 (33.56%)	
occurrences causally related to treatment / all	1 / 299	0 / 299	
deaths causally related to treatment / all	0 / 19	0 / 30	
Acute kidney injury			
subjects affected / exposed	42 / 878 (4.78%)	40 / 870 (4.60%)	
occurrences causally related to treatment / all	0 / 52	0 / 43	
deaths causally related to treatment / all	0 / 2	0 / 3	
Chronic kidney disease			
subjects affected / exposed	15 / 878 (1.71%)	9 / 870 (1.03%)	
occurrences causally related to treatment / all	0 / 15	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 4	
Diabetic nephropathy			
subjects affected / exposed	8 / 878 (0.91%)	12 / 870 (1.38%)	
occurrences causally related to treatment / all	0 / 8	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Azotaemia			
subjects affected / exposed	8 / 878 (0.91%)	9 / 870 (1.03%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 1	
Renal failure			
subjects affected / exposed	9 / 878 (1.03%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 9	0 / 1	
deaths causally related to treatment / all	0 / 6	0 / 1	
Glomerulonephritis			
subjects affected / exposed	2 / 878 (0.23%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive nephropathy			

subjects affected / exposed	2 / 878 (0.23%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal tubular necrosis			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis chronic			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder outlet obstruction			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis rapidly progressive			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydroureter			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus nephritis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritic syndrome			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive nephropathy			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post infection glomerulonephritis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal mass			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular acidosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	4 / 878 (0.46%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal chest pain			
subjects affected / exposed	2 / 878 (0.23%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	60 / 878 (6.83%)	49 / 870 (5.63%)	
occurrences causally related to treatment / all	0 / 73	0 / 60	
deaths causally related to treatment / all	0 / 5	0 / 3	
Sepsis			
subjects affected / exposed	28 / 878 (3.19%)	19 / 870 (2.18%)	
occurrences causally related to treatment / all	0 / 31	0 / 20	
deaths causally related to treatment / all	0 / 5	0 / 3	
Urinary tract infection			
subjects affected / exposed	19 / 878 (2.16%)	13 / 870 (1.49%)	
occurrences causally related to treatment / all	0 / 25	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	16 / 878 (1.82%)	13 / 870 (1.49%)	
occurrences causally related to treatment / all	0 / 19	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	12 / 878 (1.37%)	11 / 870 (1.26%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 6	0 / 5	
Peritonitis			
subjects affected / exposed	9 / 878 (1.03%)	8 / 870 (0.92%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 2	
Gastroenteritis			

subjects affected / exposed	9 / 878 (1.03%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	6 / 878 (0.68%)	8 / 870 (0.92%)	
occurrences causally related to treatment / all	0 / 8	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	7 / 878 (0.80%)	7 / 870 (0.80%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gangrene			
subjects affected / exposed	7 / 878 (0.80%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	
Influenza			
subjects affected / exposed	6 / 878 (0.68%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	7 / 878 (0.80%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	5 / 878 (0.57%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchitis			
subjects affected / exposed	3 / 878 (0.34%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	2 / 878 (0.23%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 878 (0.23%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related infection			
subjects affected / exposed	5 / 878 (0.57%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 878 (0.11%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	5 / 878 (0.57%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 878 (0.34%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	4 / 878 (0.46%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 878 (0.23%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			

subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	3 / 878 (0.34%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	3 / 878 (0.34%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	3 / 878 (0.34%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile infection			

subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	2 / 878 (0.23%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site infection			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis gangrenous			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis klebsiella			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related sepsis			

subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gas gangrene			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 878 (0.00%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal wall abscess			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis C			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous graft site infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter bacteraemia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis B			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous cystitis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis brain stem			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis viral			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune reconstitution inflammatory syndrome associated tuberculosis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site joint infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising soft tissue infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overgrowth bacterial			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cryptococcal			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic abscess			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal abscess			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site cellulitis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital infection bacterial			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	34 / 878 (3.87%)	22 / 870 (2.53%)	
occurrences causally related to treatment / all	1 / 42	0 / 36	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperkalaemia			
subjects affected / exposed	20 / 878 (2.28%)	26 / 870 (2.99%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemia			

subjects affected / exposed	18 / 878 (2.05%)	20 / 870 (2.30%)	
occurrences causally related to treatment / all	0 / 23	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	4 / 878 (0.46%)	11 / 870 (1.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	9 / 878 (1.03%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 11	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	6 / 878 (0.68%)	5 / 870 (0.57%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyponatraemia			
subjects affected / exposed	4 / 878 (0.46%)	6 / 870 (0.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	7 / 878 (0.80%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	5 / 878 (0.57%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	4 / 878 (0.46%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			

subjects affected / exposed	5 / 878 (0.57%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 878 (0.11%)	4 / 870 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	3 / 878 (0.34%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 878 (0.11%)	3 / 870 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calciphylaxis			
subjects affected / exposed	1 / 878 (0.11%)	2 / 870 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic metabolic decompensation			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 878 (0.34%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	2 / 878 (0.23%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 878 (0.11%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acidosis			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperosmolar state			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoosmolar state			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 878 (0.00%)	1 / 870 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin B1 deficiency			
subjects affected / exposed	1 / 878 (0.11%)	0 / 870 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Vadadustat	Darbepoetin alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	561 / 878 (63.90%)	565 / 870 (64.94%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	74 / 878 (8.43%)	80 / 870 (9.20%)	
occurrences (all)	90	112	
Vascular disorders			
Hypertension			
subjects affected / exposed	151 / 878 (17.20%)	186 / 870 (21.38%)	
occurrences (all)	186	237	
Hypotension			
subjects affected / exposed	49 / 878 (5.58%)	49 / 870 (5.63%)	
occurrences (all)	61	58	
Nervous system disorders			

Headache			
subjects affected / exposed	46 / 878 (5.24%)	42 / 870 (4.83%)	
occurrences (all)	52	47	
Dizziness			
subjects affected / exposed	45 / 878 (5.13%)	34 / 870 (3.91%)	
occurrences (all)	47	36	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	110 / 878 (12.53%)	89 / 870 (10.23%)	
occurrences (all)	126	98	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	114 / 878 (12.98%)	85 / 870 (9.77%)	
occurrences (all)	141	108	
Nausea			
subjects affected / exposed	87 / 878 (9.91%)	71 / 870 (8.16%)	
occurrences (all)	100	88	
Constipation			
subjects affected / exposed	74 / 878 (8.43%)	72 / 870 (8.28%)	
occurrences (all)	80	80	
Vomiting			
subjects affected / exposed	60 / 878 (6.83%)	52 / 870 (5.98%)	
occurrences (all)	67	67	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	47 / 878 (5.35%)	58 / 870 (6.67%)	
occurrences (all)	51	62	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	55 / 878 (6.26%)	45 / 870 (5.17%)	
occurrences (all)	61	46	
Arthralgia			
subjects affected / exposed	45 / 878 (5.13%)	47 / 870 (5.40%)	
occurrences (all)	49	50	
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	98 / 878 (11.16%)	94 / 870 (10.80%)	
occurrences (all)	136	127	
Upper respiratory tract infection			
subjects affected / exposed	50 / 878 (5.69%)	70 / 870 (8.05%)	
occurrences (all)	61	93	
Nasopharyngitis			
subjects affected / exposed	50 / 878 (5.69%)	48 / 870 (5.52%)	
occurrences (all)	57	60	
Bronchitis			
subjects affected / exposed	28 / 878 (3.19%)	46 / 870 (5.29%)	
occurrences (all)	31	47	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	93 / 878 (10.59%)	121 / 870 (13.91%)	
occurrences (all)	110	136	
Hyperphosphataemia			
subjects affected / exposed	64 / 878 (7.29%)	63 / 870 (7.24%)	
occurrences (all)	66	65	
Metabolic acidosis			
subjects affected / exposed	63 / 878 (7.18%)	48 / 870 (5.52%)	
occurrences (all)	72	50	
Fluid overload			
subjects affected / exposed	45 / 878 (5.13%)	55 / 870 (6.32%)	
occurrences (all)	53	69	
Hypoglycaemia			
subjects affected / exposed	46 / 878 (5.24%)	52 / 870 (5.98%)	
occurrences (all)	65	63	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2016	• Added Exclusion Criterion: "Hypersensitivity to darbepoetin or vadadustat, or to any of their excipients." • Added that the adrenal function assessment (adrenocorticotropic hormone [ACTH] stimulation test) was to be conducted in a subset of 200 subjects in the European Union (100 subjects from the vadadustat treatment group and 100 subjects from the darbepoetin alfa treatment group) across the 2 non-dialysis-dependent chronic kidney disease (NDD-CKD) studies, AKB 6548-CI-0014 and AKB 6548-CI-0015. • Defined that the study completion date (end of trial) was to take place when 631 major adverse cardiovascular events (MACE) events had accrued over the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015). • Clarified that the double-barrier method should have been practiced starting at Screening Visit 1, throughout the study, and for 30 days after the last dose of study drug. • Added that "In case of substantial protocol amendment, the sponsor will obtain approval from responsible Regulatory Authorities before implementation."
18 April 2016	• Updated Exclusion Criteria. • Added hospitalization for heart failure (HF) as an adjudicated safety endpoint in addition to MACE and thromboembolic events. • Clarified that the darbepoetin alfa dosing adjustment guidelines were based on the approved local product label for adult subjects with CKD not on dialysis. • Allowed subjects who transitioned to hemodialysis or peritoneal dialysis during the study to continue to receive study drug (vadadustat or darbepoetin alfa). This is supported by acceptable safety data from a recently-completed Phase 2 trial of vadadustat in subjects with DD-CKD. • Introduced a binary causality system (i.e., "related" or "unrelated") for clinical trial investigators to assign causality of adverse events to study drugs in accordance with recommendations from the Council for International Organizations of Medical Sciences (CIOMS) VI Working Group. • Following discussions with the United States Food and Drug Administration (US FDA), it was requested that the sparse pharmacokinetic (PK) sampling scheme be described and justified. The results of PK simulations indicated that collection of a sample between 0.25 to 1 hour after administration of the first dose along with sparse samples collected during Weeks 4, 12, 28, and 52 would provide additional information to help characterize the population PK and PK/pharmacodynamic (PD) relationships. • Adverse event reporting related to critically increased liver function test results was aligned with the US FDA Drug-Induced Liver Injury (DILI) guidelines to provide instructions to study sites regarding reporting for improved consistency and case quality. • Added visit windows to provide flexibility to the subjects and the study sites during scheduling of study visits. • Clarified definitions for renal events to improve understanding and site compliance.

08 June 2017	• Updated the study design. • Updated Exclusion Criteria. • Increased number of total sites in efforts to increase enrollment. • Updated vadadustat dosing and dose adjustment guidelines to clarify that subjects receiving 1 tablet of dosing prior to interruption were to resume treatment with 1 tablet after interruption. • Clarified that intravenous (IV) iron may have been given to subjects who were intolerant or not responding well to oral iron. • Updated Summary of Clinical Experiences section to reflect information from recently completed trials. • Added details on Executive Steering Committee. • To clarify darbepoetin alfa administration and accountability, the following details were added: o Darbepoetin alfa was changed to be administered per the label. o Darbepoetin alfa was changed to allow doses to be self-administered or administered by health care professional at the clinics, site facility, or at subject's home according to the investigator's determination and local practice. o Added additional information on return of darbepoetin alfa for drug accountability and compliance assessment. • Revised Laboratory Evaluations section with details on sample collection. • Provided clarity regarding the study analysis populations.
18 January 2018	• Updated to reflect information from recently completed trials and for alignment with vadadustat Investigator's Brochure. • Added several key secondary, other secondary efficacy endpoints and safety endpoints to align with the Statistical Analysis Plan (SAP). • Section 7.4.1 Retesting was updated for simplification. • Updated to add Lack of Efficacy as a reason for permanent discontinuation of study drug or study participation for accurate data capture. • Revised to clarify that all enrolled subjects in this study were to have completed (at least) the Week 36 visit. • Revised Dosing and Dose Adjustment Guidelines section to guide Investigators. • Updated to align with published guidelines to prescribe iron supplementation and for initiation of ESA rescue. • Updated Dosing Compliance section to specify a range of 80% to 120%. • Updated Prior and Concomitant Therapy section was to include text clarifying that if the duration of the screening period was less than 30 days, all medications taken within 30 days prior to first dose of study drug were to be recorded. • Added Year 2-4 Monthly Hb monitoring section. • Updated Serious Adverse Events section to require all new and recurrent malignancies to be reported as a Serious Adverse Events (SAEs) to standardize reporting. • Updated Special Situations section to add text defining overdose of study drugs. • Updated Sample Size for Primary Efficacy Endpoint section to reflect a change in the non-inferiority margin from -0.5 grams per deciliter (g/dL) to -1.0 g/dL. • Updated Sample Size for the Primary Safety Endpoint section with enrollment projections as well as median study drug exposure times. • Updated Missing Data section to align with SAP. • Updated Subgroups section to pre-specify key subgroups for subsequent analysis. • Updated Analysis of Adverse Events section.

13 September 2018	• Updated with revised subject number. • Clarified that all enrolled subjects were allowed to complete the primary efficacy period prior to global study completion (GSC). • Clarified procedures at time of GSC. • Emphasized importance of continuing to follow subjects through GSC. • Updated details related to drug interruption. • Updated timing of End of Trial (EOT) visit and Follow-up visit. • Updated with all options to be considered by the Investigator before a subject withdrew consent. • Included all options available to the Investigator to follow subjects that permanently discontinued study drug. • Detailed steps to support sites in efforts to identify subjects lost to follow-up. • Updated with information for which the Sponsor/Clinical Research Organization will remain blinded. • Clarified restart of study drug after erythropoiesis-stimulating agent (ESA) rescue/red blood cell transfusion. • Provided clarity on study drug dosing after ESA administration. • Added guidance on managing concomitant use of statins with vadadustat. • Updated collection time for AEs. • Added details on managing subjects that permanently stopped study drug and managing subjects on study drug at GSC. • Defined the end of study assessments that documented subject status at GSC or at the time of subject withdrawal or when subject was deemed lost to follow-up or upon death. • Added guidance on managing subjects who developed malignancy while on study drug. • Indicated that Sponsor had defined events that were classified as serious regardless of their assessment. • Clarified AE reporting period. • Updated to reflect how Baseline was calculated for Hb. • Updated noninferiority margin. • Updated definition for primary safety endpoint and how non-inferiority was established between treatment groups. • Defined full analysis population. • Updated with use of analysis of covariance (ANCOVA) with multiple imputation, stratified by the randomization strata and using Baseline Hb as the covariate.
18 December 2018	• Updated to include reference to the Pharmacy Manual which provides further details on storage and managing temperature excursions. • Updated to provide further guidance regarding concomitant use of simvastatin drug interactions with vadadustat. • Provided guidance regarding concomitant use of breast cancer resistance protein (BCRP) substrates with vadadustat. • Updated with recent results of investigative toxicology studies. • Liver function tests were increased in Year 2, 3, and 4 to include Week 64, 88, 116, 140, 168, and 192.
26 February 2019	• Updated to include a reference to Study Drug Stopping Rules for management of subjects with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) abnormalities. • Include the table of liver function test results that would require permanent discontinuation of vadadustat. • Updated to exclude subjects with elevations in ALT or AST >3 times the upper limit of normal (ULN) with an elevation of total serum bilirubin >2 times the ULN from conditions of temporary discontinuation, as this is now a condition for permanent discontinuation. • Updated to include information defining designated medical events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported